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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,751	12/14/2005	Olivier Lambert	ON/4-33220A	3065

1095 7590 12/11/2007

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
HA, JULIE	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
12/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,751	LAMBERT ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 10-14* is/are pending in the application.

4a) Of the above claim(s) *10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment after Non-final rejection filed on October 18, 2007 is acknowledged. Claims 7-8 have been cancelled. Claims 1-6 and 10-14 are pending in this office action. Applicant elected Group I (claims 1-8 and 10) drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analogue and elected peptide of formula II in the reply filed on March 21, 2007. Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, therefore, the election has been treated as an election without traverse and is deemed proper. The Restriction requirement is made FINAL. Claim 10 remains withdrawn from further consideration as being drawn to a nonelected species Claims 1-6 and 11-14 are examined on the merits in this office action.

Withdrawn Objections

1. Objections to claims 6-8 cited in the previous office action are hereby withdrawn due to Applicant's amendments.

Withdrawn Rejections

2. Claims 7-8 have been cancelled. Therefore, any rejections to these claims are moot. Rejections to claims 7-8 are hereby withdrawn due to Applicant's amendments.

3. Rejections under 35 U.S.C. 102(b) and (e) are hereby withdrawn due to Applicant's arguments.

4. Rejections under 35 U.S.C. 103(a) are hereby withdrawn due to Applicant's arguments. However, after further consideration, new rejections follow below.

New Objection

5. Claim 1 is objected to due to following minor informalities: Applicant is advised to use better language to make the claim clear that the pharmaceutical composition for parenteral administration is a combination of somatostatin analog and tartaric acid. The following are some suggestions to make the claim clear:

1). "A pharmaceutical composition for parenteral administration comprising tartaric acid and somatostatin analogue comprising an amino acid sequence of formula I..."

or

2) "A pharmaceutical composition for parenteral administration comprising somatostatin analogue comprising an amino acid sequence of formula I...in combination with tartaric acid..."

or

3) "(a) A pharmaceutical composition for parenteral administration comprising somatostatin analogue comprising an amino acid sequence of formula I...,and"

"(b) tartaric acid."

Or

4) "A pharmaceutical composition for parenteral administration comprising somatostatin analogue comprising an amino acid sequence of formula I...in free form, salt form or protected form;"

"and tartaric acid."

New Rejection

35 U.S.C. 112, 2nd

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1 recites the limitation "the amino acid sequence" in line 2 of the claim. There is insufficient antecedent basis for this limitation in the claim. "The amino acid" sequence should be changed to "an amino acid" sequence.

35 U.S.C. 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly-owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al (US Patent # 5059587).

12. The instant claim is drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analogue comprising the amino acid sequence of formula I and tartaric acid.

13. Yamamoto et al teach a nasal administration powder composition containing a physiologically active peptide as an active ingredient can be efficiently absorbed through nasal mucosa by the addition of a water-soluble organic acid as an absorption promoter (see abstract). The reference further teaches that injections often cause pains and are not preferred (see column 1,

lines 18-20). The reference teaches that the physiologically active peptides which are active ingredients in the composition include peptide hormones, proteins and enzymes which have physiological activity such as calcitonin gene related peptides (CGRP), calcitionin, parathyroid hormone (PTH), insulin, somatostatin, growth hormone, secretin, gastrin, vaspressin, oxytocin...(see column 2, lines 25-40). The reference lists about 20 physiologically active peptides. The reference further teaches that the water-soluble organic acids are succinic acid, tartaric acid, citric acid, fumaric acid...(see column 3, lines 23-28 and claim 1). Furthermore, the reference teaches that the nasal administration powdered composition is superior to the conventional liquid preparations for nasal administration of peptide hormone in terms of stability of active ingredients...(see column 4, lines 42-54). Furthermore, the reference teaches that nasal administration powdered composition is much superior to the conventional nasal administration powdered preparations in absorbability through nasal mucosa (see column 4, lines 55-58 and column 1, lines 50-54, "Summary of the Invention"). This reads on claim 1, since nasal administration is a species of parenteral administration. The difference between the reference and the instant claim is that the reference does not teach the somatostatin analog comprising the amino acid sequence of formula I.

14. Therefore, it would have been obvious to one of ordinary skilled in the art to substitute the somatostatin taught in Yamamoto et al for the somatostatin analog, since these analogs may be more potent. There is a reasonable expectation of success since Yamamoto et al teach that tartaric acid and active

peptide complex is more stable and has higher absorbability through nasal administration. Further, nasal administration would not cause the pains of injections as disclosed by Yamamoto et al.

15. Claims 2-5 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al (US Patent # 5059587) in view of Albert et al (WO 02/10192).

16. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog comprising the amino acid sequence of formula I (in aspartate di-salt form) and II and tartaric acid, and a pharmaceutical composition wherein the somatostatin analog is cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro]Phg-DTrp-Lys-Tyr(4Bzl)-Phe].

17. Yamamoto et al teach a nasal administration powder composition containing a physiologically active peptide as an active ingredient can be efficiently absorbed through nasal mucosa by the addition of a water-soluble organic acid as an absorption promoter (see abstract). The reference further teaches that injections often cause pains and are not preferred (see column 1, lines 18-20). The reference teaches that the physiologically active peptides which are active ingredients in the composition include peptide hormones, proteins and enzymes which have physiological activity such as calcitonin gene related peptides (CGRP), calcitionin, parathyroid hormone (PTH), insulin, somatostatin, growth hormone, secretin, gastrin, vaspressin, oxytocin...(see column 2, lines 25-40). The reference lists about 20 physiologically active peptides. The reference

further teaches that the water-soluble organic acids are succinic acid, tartaric acid, citric acid, fumaric acid...(see column 3, lines 23-28 and claim 1). This reads on claim 1. Furthermore, the reference teaches that the nasal administration powdered composition is superior to the conventional liquid preparations for nasal administration of peptide hormone in terms of stability of active ingredients...(see column 4, lines 42-54). Furthermore, the reference teaches that nasal administration powdered composition is much superior to the conventional nasal administration powdered preparations in absorbability through nasal mucosa (see column 4, lines 55-58 and column 1, lines 50-54, "Summary of the Invention"). Additionally, the reference teaches that the water-soluble organic acid is at least in such an amount that the aqueous solution of the powdered composition is acidic...water soluble organic acid is added until the pH is not more than about 4 when the composition (10 mg) is dissolved in water (1 ml) (see column 4, lines 1-7). Furthermore, the reference teaches that to the resulting lyophilized powder is added water-soluble organic acid or are added water-soluble organic acid and diluent, and these are mixed to obtain a homogeneous composition (see column 4, lines 23-27). The difference between the reference and the instant claims is that the reference does not teach cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro]Phg-DTrp-Lys-Tyr(4Benzyl)-Phe].

18. However, Albert et al discloses cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro]Phg-DTrp-Lys-Tyr(4Benzyl)-Phe], optionally in protected form, or a pharmaceutically acceptable salt or complex thereof (see abstract). Additionally, the structural formula of instant claim 2 is shown in paragraph 2 and described in paragraph 3

as cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro]Phg-DTrp-Lys-Tyr(4Bzl)-Phe] and is referred to as compound A (see paragraphs [0002] and [0003], structure of formula on p. 1 and claim 1). The reference further teaches that compound A or a pharmaceutically acceptable salt or complex thereof may be administered by any conventional route, for example parenterally (see p. 15, paragraph 4). Furthermore, the reference teaches that compound A may exist in free or salt form. Preferred salt are lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt (see p. 3, paragraph 4).

19. Therefore, it would have been obvious for one of ordinary skill in the art to combine the teachings of Yamamoto et al and Albert et al to produce a pharmaceutical composition for parenteral administration comprising a somatostatin analog and tartaric acid, because both prior arts teach a pharmaceutical composition for parenteral administration of physiologically active peptide (somatostatin) and analogs may be more potent. There is a reasonable expectation of success since injections often cause pain (see Yamamoto, column 1, line 18) and powdered nasal administration composition containing peptide hormone as an active ingredient and tartaric acid (organic acid) is superior in safety and stability and from which the active ingredient can be fully absorbed through the nasal cavity (see Yamamoto, column 1, lines 50-54). Furthermore, Yamamoto et al list about 20 active peptide, thus one of ordinary skilled in the art would at once envisage the composition of somatostatin and tartaric acid for nasal administration composition. Furthermore, Yamamoto et al teach that the

conventional liquid preparations for nasal administration of peptide hormone, surface active agents are used as absorption promoter, which are highly irritative against nasal mucosa and preservatives are used for preventing contamination with microorganisms, which cause harmful effects...However, nasal administration powdered composition using tartaric acid as absorption promoter suffer from no such problems (see column 4, lines 45-54).

20. Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al (US Patent # 5059587) in view of Albert et al (WO 02/10192) as applied to claims 1-5 and 11-12 above, and further in view of Stalla et al (European Journal of Endocrinology, 1994, 130: 125-131).

21. The instant claims are a method of treating Cushing's Disease comprising administering a pharmaceutical composition, wherein the somatostatin analog is cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro}-Phg-DTrp-Lys-Tyr(4Bzl)-Phe].

22. The teachings of Yamamoto et al and Albert et al (WO 02/10192) are described, supra. The difference between the reference and the instant claims is that the reference does not teach a method of treating Cushing's Disease.

23. However, Stalla et al teach that somatostatin analog octreotide (SMS 201-995) had different effects in vivo and in vitro in Cushing's disease (see Title). The reference teaches that octreotide could inhibit the ACTH release from human corticotropic adenoma cells in vitro but had no suppressive effect on ACTH levels of patients with Cushing's disease in vivo (see abstract). The reference teaches that octreotide suppressed ACTH serum levels in patients with adrenal

insufficiency (Addison's disease) and in patients with Nelson's syndrome. This indicates that human corticotropic adenoma cells contain somatostatin receptors (see p. 125). The reference explains that since octreotide suppressed ACTH serum levels in both Addison's and Nelson's disease, the in vivo and in vitro discrepancy with Cushing's disease may be due to a somatostatin receptor down-regulation by cortisol at the hypercortisolemic state in vivo (see p. 125, 2nd paragraph).

24. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Albert et al, Yamamoto et al and Stalla et al to treat Cushing's disease. Albert et al teach somatostatin analogs, Yamamoto et al teach nasal administration powder composition containing a physiologically active peptide, such as somatostatin, and Stalla et al teach somatostatin analog in treating Cushing's Disease in vivo and in vitro, therefore, there is a reasonable expectation of success, since all teach somatostatin or its analog. And since Stalla et al teach treatment of Cushing's Disease, there is motivation of success, since all prior arts teach somatostatin or its analogs, and Yamamoto et al teach a noninvasive (nasal administration) means of administration. Additionally, since Albert et al teach the compounds are useful for the treatment of malignant cell proliferative diseases, e.g. cancer tumors, particularly tumors bearing the somatostatin receptor types targeted by the compounds (see p. 20, 3rd paragraph) and that corticotropic adenoma cells contain somatostatin receptors (see Stalla), it would have been obvious to use somatostatin analogs for treatment for Cushing's disease.

25. Claims 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Albert et al (WO 02/10192) in view of Kamber B (US Patent # 4603120) and further in view of Bodmer et al (US Patent # 5639480).

26. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a somatostatin analog wherein the composition is buffered by an acetate/acetic acid, lactate/lactic acid or glycine/HCl buffer to about pH 4 to about pH 4.5.

27. Albert et al discloses cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro]Phg-DTrp-Lys-Tyr(4Benzyl)-Phe], optionally in protected form, or a pharmaceutically acceptable salt or complex thereof (see abstract). Additionally, the structural formula of instant claim 2 is shown in paragraph 2 and described in paragraph 3 as cyclo[{4-NH_2-C_2H_4-NH-CO-O)Pro]Phg-DTrp-Lys-Tyr(4Bzl)-Phe] and is referred to as compound A (see paragraphs [0002] and [0003], structure of formula on p. 1 and claim 1). This reads on claim 5. The reference further teaches that compound A or a pharmaceutically acceptable salt or complex thereof may be administered by any conventional route, for example parenterally (see p. 15, paragraph 4). This further reads on claim 5. Furthermore, the reference teaches that compound A may exist in free or salt form. Preferred salt are lactate, aspartate, benzoate, succinate and pamoate including mono- and di-salts, more preferably the aspartate di-salt (see p. 3, paragraph 4). The difference between the reference and the instant claims is that the reference does not teach the pH of about 4 to about 4.5 and the composition is buffered by an acetate/acetic acid, lactate/lactic acid or glycine/HCl buffer.

28. However, Kamber B teach cyclopeptides of the somatostatin type and processes for their manufacture, and to pharmaceutical preparations containing these compounds and the use of these compounds or preparations for therapeutic purposes (see column 1, lines 7-11). Furthermore, the reference teaches the preparations may be used especially for parenterally administration (see column 15, lines 51-54). Furthermore, the reference teaches that preparations for parenteral administration in single-dose form...contain a buffer, for example a phosphate buffer, that is to maintain the pH between approximately 3.5 and 7, and also sodium chloride, mannitol or sorbitol for adjusting the isotonicity (see column 16, lines 1-9). The difference between the prior arts and the instant claims is that the reference does not teach the acetate buffer system.

29. However, the Bodmer et al teach microparticles comprising a somatostatin or an analog or derivative thereof (ocetretide) in a buffer system that may be prepared from acidic buffers such as phosphate buffer, acetate buffer and the like and the buffer may be from pH 2 to 8 with a pH 4 preferred (see abstract and column 9, lines 3-8). Further, the reference teaches that the microparticles can be administered in conventional manner, e.g. subcutaneous or intramuscular injection (see column 12, lines 6-7).

30. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Albert et al, Kamber and Bodmer et al to administer the somatostatin in a buffer system containing acetate because for parenteral use, buffers such as phosphate and acetate can be used. There is a reasonable

expectation of success, since all prior arts teach parenteral administration of somatostatin or analog thereof and Kamber teaches that parenteral administration in single-dose form contain a buffer, for example, a phosphate buffer, that is to maintain the pH between approximately 3.5 to 7 and Bodmer et al teach that emulsion may be buffered with a buffer which is non-detrimental to the peptide and the polymer matrix material (see column 9, lines 5-7). Thus, it would have been obvious to provide the composition in a buffer system (acetate buffer) to maintain the activity and inhibit the degradation of the somatostatin.

Conclusion

31. No claims are allowed.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public

PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Julie Ha
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AU 1654

12/10/07
ANISH GUPTA
PRIMARY EXAMINER